Combined Modality Treatment with Chemotherapy and Radiotherapy for Primary Gastric Lymphoma

A Thesis Submitted for the partial fulfillment of
MD Degree in Clinical Oncology and Nuclear Medicine

Presented by

Haytham Ahmed Abdelkader Ibrahim
M.B.,B.ch., M.Sc.
Faculty of Medicine, Ain Shams University

Supervised by

Prof. Dr. Laila Faris Matta
Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine, Ain Shams University

Prof. Dr. Manal Moawad Abdel-Wahab
Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine, Ain Shams University

Dr. Walid Abdel-Monaem Bayomy
Ass. Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2011

ACKNOWLEDGEMENT

*First of all I thank **ALLAH** for granting me the power to proceed and accomplish this work*

*I would like to express my endless gratitude and appreciation to **Prof. Dr. Laila Faris Matta,** Professor of Clinical Oncology and Nuclear Medicine Faculty of Medicine, Ain Shams University, For giving me the honor of working under her supervision and her great effort for suggesting and planning this work and providing me a lot of encouragement through out this work and always.*

*It is with my pleasure to acknowledge with sincere thanks and appreciation the great effort, help and encouragement afforded to me by **Prof. Dr. Manal Moawad Abdelwahab ,** Professor of Clinical Oncology and Nuclear Medicine Faculty of Medicine, Ain Shams University, for her much valuable suggestions, fruitful discussions and guidance during the course of the work presented in this thesis.*

*I would like to express my profound gratitude to **Dr. Walid Abdel-Monaem Bayomy,** Assistant Professor of Clinical Oncology and Nuclear Medicine Faculty of Medicine, Ain Shams University for his helpful guidance and Kind instructions during all the work in order to come in this form.*

Great thanks to the staff members of the department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University and to my Colleagues for their kind sympathy during the accomplishment of this work. Also I would

like to express my great thanks to my colleagues in Ahmed Maher Teaching Hospital.

I cannot find adequate words to express my sincere gratitude to ***my family*** *for their continuous help, support and loving encouragement throughout my study.*

Dedication
This work is dedicated to

The Soul of My Father
The soul of Prof. Dr. Laila Fares
To My Mother
My wife
My Kids
Mariam,
Karim,
&
Yousef

Introduction:

Primary gastrointestinal lymphoma represents the most common location of extranodal lymphoma with bulk of disease manifesting within the gastrointestinal tract and contiguous lymph nodes ***(Dickson et al, 2006).***

Gastrointestinal lymphoma compromises a group of distinct clinicopathological entities. Differences in life style and environmental factors between countries could account for the variety in the distribution of the disease ***(Rambaud, 2001).***

The stomach represents 50-75% of the gastrointestinal tract localizations ***(Zucca, 2006).***

Primary gastric lymphomas are the most common extranodal non-Hodgkin's lymphomas and are divided into indolent (low grade) and aggressive (high grade) types. They are mainly diseases of middle age, with a male predominance reported by most of the studies ***(Novakovi et al, 2006).***

Primary gastric lymphoma may originate from either T-cells or B-cells, (MALT-Lymphoma), follicular lymphoma, mantle cell lymphoma, or other aggressive lymphomas may be found. B-cell primary gastrointestinal lymphoma tends to present at lower stage with fewer complications and have better prognosis than T-cell lymphoma ***(Emmanouilides and Casciato, 2004).***

Controversy remains regarding the best treatment for early stages of the disease. Chemotherapy, Surgery and combination have been studied and shared almost comparable results with survival rate of 70-90%. However, chemotherapy possesses the advantage of preserving gastric anatomy (***AL-Akwaa et al, 2004).***

Recent years have seen a dramatic paradigm shift in the treatment approach to the most common gastrointestinal lymphomas, i.e. DLBCL and MALT lymphoma of the stomach. While surgery had been the main stay of treatment for decades, it has now virtually been abolished due to the absence of a beneficial effect as compared to conservative therapy ***(Raderer, 2007).***

The discovery of an association between Helicobacter pylori (HP) and gastric MALT lymphoma and the subsequent reports of lymphoma regression following HP-eradication have revolutionized treatment options for such patients. HP-eradication is currently considered standard first-line therapy in patients with gastric MALT lymphoma and evidence of HP-infection, with complete responses being obtained in roughly 75% of selected patients ***(Fischbach et al, 2006)***

Also combined modality treatment by chemo-radiation for localized gastric lymphoma is associated with a low risk of treatment related complications, with avoidance of long term sequelae after gastric resection ***(Schmidt, 2004).***

In DLBCL of the stomach, the association with HP-infection is less pronounced than in MALT lymphoma at roughly 50% of patients. However, recent data have shown impressive responses to HP-eradication also in patients with gastric DLBCL and HP-infection. While gastric DLBCL had also been subjected to surgery in order to prevent bleeding and perforation during subsequent chemotherapy and radiation, it has been demonstrated that such prophylactic surgery is not necessary with the consequent application of a high dose proton pump inhibitors for the whole duration of therapy. In addition, the relapse rate and survival are not beneficially influenced by additional surgery, while quality of life may be severely impaired. Most large studies have been performed combining anthracycline-based chemotherapy and radiation therapy. ***(Raderer, 2007).***

Aim of the Work:

First end point of the study is evaluation of Response Rate (RR) and second end points are evaluation of the two years Relapse Free Survival (RFS) and Overall Survival (OS).

Epidemiology and Etiology

Epidemiology:

The word ‘lymphoma' was first used by Virchow to indicate a tumor arising *de novo* in lymph nodes, but was coined long before there was any real comprehension of the biology of the tumors we now know by this name. We now recognize that neoplasm's arising from the cells of the lymphoreticular, or immune system, can involve almost any organ or tissue of the body, the majority of which are kept under surveillance for foreign substances or micro-organisms by lymphocytes. Virchow also introduced the idea of ‘cellular pathology', and since the mid-nineteenth century our understanding of the nature, function, and pathology of lymphoid tissue has focused more and more on cells rather than tissues. A great deal has been learned of the ontogeny of lymphocytes as well as the cellular interactions that form the basis of the immune response, thus the original notion that lymphomas could potentially arise from any of the various elements of lymph nodes (including endothelial cells), was replaced by the concept that lymphomas are neoplasm's of the cells of the immune system. Today, the group of tumors commonly referred to as the non-Hodgkin's lymphomas is generally considered to include only neoplasm's of lymphocytes or their precursors ***(Magrath, 2002).***

Lymphomas, a heterogeneous group of malignancies arising in the lymphoid tissue, account for over 3% of cancers occurring world wide. Most lymphomas are B-cell in origin, with a minority being T-cell. A few inherited disorders, immunosuppressive drug therapies and certain viruses are known about etiology of Lymphomas. However, for the most part, little is currently known about the etiology of lymphomas ***(Eleanor and Eve, 2007).***

NHL is one of the two malignancies with greatest increase in incidence in the Western world in recent years (Melanoma is the other), and the fifth most common of all malignancies (following Prostate, breast, lung and colorectal) and the Sixth most common cause of cancer related deaths (after lung, colorectal, breast, prostate and pancreas) ***(Prosnitz and Mauch, 2004).***

A striking increase in NHL incidence rates has occurred over the past four decades that has been referred to as an epidemic of NHL. The reasons for this are not entirely clear. Although there have been increases in most histologies, the largest increases have occurred in patients with aggressive lymphomas. This increase in primary central nervous system (CNS) lymphoma is in part related to the occurrence of primary CNS lymphomas in patients with acquired immunodeficiency syndrome (AIDS), although the increase in incidence began before the AIDS epidemic, and incidence rates have increased in non-AIDS populations. Geographic differences in histologic subtypes of NHL have been noted. Examples include the endemic form of Burkitt's lymphoma, which is seen most

commonly in children in equatorial Africa. Higher rates of gastric lymphoma have been reported to occur in northern Italy ***(Friedberg et.al, 2008).***

According to the Surveillance Epidemiology and End Results (SEER) data, the incidence has been rising approximately 4% a year and represents a 150% increase between the 1940s and the 1980s. In absolute numbers, this represents approximately 56,000 new cases and 20,000 deaths of NHL in the United States each year ***(Wilson and Armitage, 2008).***

Several hypotheses have been advanced to explain the increasing frequency of NHL. Some of the increase may be artificial, as new NHL classification systems and advances in molecular techniques have led to a diagnosis of NHL in some patients previously diagnosed with pseudo-lymphoma or atypical lymphoid hyperplasia. This is especially true for the lymphomas of mucosa associated lymphoid tissue (MALT) and certain T-cell lymphomas. In addition to improved imaging techniques have led to more NHL diagnosis ***(Prosnitz and Mauch, 2004).***

NHL is diagnosed in 11.4 and 8.2 of 100 000 men and women respectively each year. Across all nations, more men than women are diagnosed with NHL, incidence increases with age, and data from the USA suggest that the incidence is greater among whites than blacks ***(Eleanor and Eve, 2007).***

Malignant lymphoma, which comprises both Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL), is the third most common malignancy in childhood. Among children younger than 15 years of age, there is a slight predominance of NHL, whereas Hodgkin's lymphoma is more frequent if children up to 18 years of age are included. There are approximately 500 newly diagnosed cases of pediatric NHL in the United States each year ***(Sandlund and Onciu, 2008).***

In Europe, lymphomas were about 4.2% of all incident cases of cancer, and about 3.8% of all cancer deaths in 2004 **(**Table 1 and 2) ***(Boyle and Ferlay, 2005).***

Table (1): Estimates of numbers of incident cases of cancer in Europe, both sexes combined (2004) (in thousands) ***(Boyle and Ferlay, 2005).***

Site	Cases	%
All sites except non-melanoma skin	2886.8	100.0
Lung	381.5	13.2
Colon and rectum	376.4	13.0
Breast	370.1	12.8
Prostate	237.8	8.2
Stomach	171.0	5.9
Uterus	133.8	4.6
Lymphomas	121.2	4.2
Oral cavity and pharynx	97.8	3.4
Leukemia	75.6	2.6
Larynx	46.1	1.6
Esophagus	43.7	1.5

Table (2): Estimates of numbers of cancer deaths in Europe, both sexes combined (2004) (in thousands) ***(Boyle and Ferlay, 2005).***

Site	Deaths	%
All sites except non-melanoma skin	1711.0	100.0
Lung	341.8	20.0
Colon and rectum	203.7	11.9
Stomach	137.9	8.1
Breast	129.9	7.6
Prostate	85.2	5.0
Lymphomas	65.2	3.8
Leukemia	52.6	3.1
Uterus	49.3	2.9
Oral cavity and pharynx	40.1	2.3
Esophagus	39.5	2.3
Larynx	24.5	1.4

From data registry in Ain shams university oncology centre about 7662 new cancer patient from 2001-2005, the Non Hodgkin lymphoma cases were about 340 case (4.43%).

Gastrointestinal Non Hodgkin lymphoma:

The term primary extranodal non-Hodgkin's lymphoma (PE-NHL) refers to lymphomas which present with disease at any organ or tissue other than lymph nodes or spleen; the

symptoms at initial presentation are caused mainly from extranodal involvement and after routine staging procedures, the extranodal involvement remains the clinically dominant site of the disease. PE-NHL comprises ~25%–40% of non-Hodgkin's lymphoma (NHL) and may occur at any organ ***(Economopoulos et al, 2005).***

Primary non-Hodgkin's lymphoma of the gastrointestinal tract is the most commonly involved extranodal site and represents 10%–15% of all NHL cases and 30%–40% of all extranodal sites. The most commonly involved site is the stomach (60%–75% of cases), followed by the small bowel, ileum, cecum, colon and rectum ***(Koch et al, 2001).*** All histological categories of nodal lymphomas may also arise in the gastrointestinal (GI), but the main two histological subtypes (>90% of cases) are mucosa-associated lymphoid tissue (MALT) NHL and diffuse large B-cell NHL (DLBCL) ***(Papaxoinis et aL, 2006).***

Neoplastic involvement of the gastrointestinal tract is the most common primary site of extranodal lymphoma. In fact, primary gastrointestinal lymphoma accounts for at least 15 percent of all Non-Hodgkin's lymphoma, and the incidence, mainly for gastric lymphoma, is rapidly increasing. The primary lesion is in the stomach in approximately 60 %of cases, in the small bowel in 30 %, and the remaining 10 to 12 % of cases present in the large bowel. Approximately three-quarters of the patients will show an intermediate- or high-grade histology. Primary T-cell lymphomas in the gastrointestinal tract are

exceedingly rare and are generally a complication of a longstanding, gluten-sensitive enteropathy ***(Gisselbrecht and Solal-Céligny, 2002).***

Any histological subtype of lymphoma can arise in the stomach, but the main two histological subtypes (>90% of cases) are MALT NHL and DLBC NHL. *Helicobacter pylori* infection has been implicated in the pathogenesis of MALT PG-NHL ***(Nakamura et al, 1997)***. But its role in gastric DLBC NHL is controversial ***(Chen et al, 2005).***

Primary gastric lymphomas represent about 5% of all gastric cancers, second in frequency after adenocarcinoma ***(Ferrucci and Zucca, 2007).***

Lymphomas of the stomach are considered primary if the main bulk of the disease is located at this site. They are Non Hodgkin's Lymphomas (NHL), typically either Diffuse large B–Cell Lymphomas (DLBCL) or extranodal Marginal Zone Lymphomas of mucosa associated tissues (MZL). Follicular lymphomas and mantle cell lymphomas are less common in the stomach, the later often presents as multiple lymphomatous polyps of the gastrointestinal tract. DLBCL, an aggressive NHL subtype, represents about 60% of localized gastric lymphoma. A quarter of gastric DLBCL contains an MZL component, with DLBCL presumed to arise from MZL as a transformation. MZL is an indolent lymphoma that represents 40% of gastric lymphomas. Follicular lymphoma, mantle cell lymphoma, and peripheral T-cell lymphoma account for less than 5% of primary gastric NHL ***(Koch et al, 2005).***